New Developments in Opportunistic Infections: Interactive Case-Based Panel Discussion

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IAS–USA

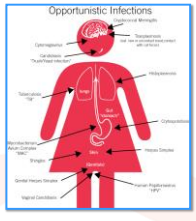
Learning Objectives

After attending this presentation, learners will be able to:

- Describe the current trends in opportunistic infections (OIs) in the U.S.
- List the more common OIs in the U.S.
- Describe the concept of immune reconstitution inflammatory syndrome (IRIS)
- Identify appropriate resources for diagnosing and managing OIs

Overview

- Opportunistic Infections
  - A brief history and where we are now.
  - What's new:
    - Providers
    - Patients
    - Pathogens
    - Diagnostic tools
  - Contemporary cases



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Limitations of the presentation

- It is just a talk.
- There are over 40 OIs listed in the guidelines.
- It is an attempt to give a general overview with direction to find the details.
  - The clinician should feel comfortable developing a coherent work up based on patient centered evaluation, then look up the treatment.
- It is experience based.

Pablo A.

- Thirty-six-year-old Vietnam veteran who become chronically ill in 1982.
- Over about 11 months he developed weight loss, fatigue, nights sweats, dysphagia, and decreased memory.
- In September of 1982 he was diagnosed with HTLV III infection.
- His initial CD4 count was 9 cells/mm^3.
- He died in December 1985 in Perth Amboy New Jersey.

AIDS 1985- One Patient's Experience

- 322 IV insertions
- 14 hospital admissions
- 11 months of hospital stay
- 60 phlebotomies
- 32 chest x-rays
- 5 CT scans of head
- 3 abdominal ct scans
- 6 bronchoscopies
- 8 intubations
- 4 lumbar punctures
- 3 bone marrows
- 5 cycles of chemo
- 2 lymph node bx

AIDS 1985- One Patient's Experience

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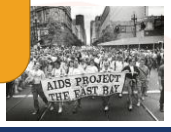
- tures
- vs
- emo

Pablo's Illnesses included: PCP (3), MAC, esophageal candidiasis, disseminated VZV, cryptococcal meningitis, wasting, dementia, cardiomyopathy, NHL.



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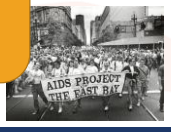
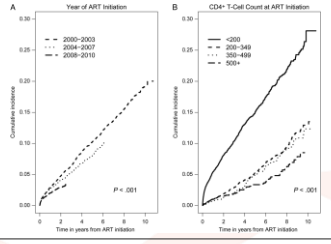
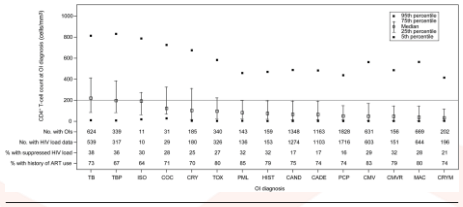
Pablo never received a medication to treat his HIV or prevent any of his OI's.



So where are we now?



From: Incidence of AIDS-Defining Opportunistic Infections in a Multicohort Analysis of HIV-Infected Persons in the United States and Canada, 2000–2010
J Infect Dis. 2016;214(6):862-872. doi:10.1093/infdis/jiw085
J Infect Dis | Published by Oxford University Press for the Infectious Diseases Society of America 2016. This work is written by (a) US Government employee(s) and is in the public domain in the US



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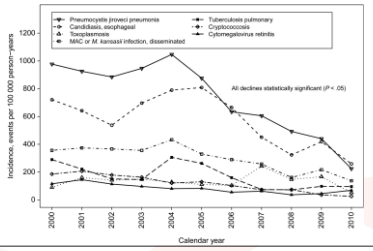

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- *Not all HIV infections are diagnosed, and once diagnosed many persons have already experienced substantial immunosuppression.*
- CDC estimates that in 2015, 15% of the people with HIV in the United States were unaware of their infections. Among those with diagnosed HIV, more than 50% had had HIV for more than 3 years and approximately 20% had a CD4 T lymphocyte (CD4) cell count <200 cells/mm^3 (or <14%) at the time of diagnosis.

So who gets OIs?

- Newly diagnosed with HIV and AIDS diagnoses coinciding.
- Patients with advanced disease lost to care.
- Global patients.
- Poorly managed patients in care.

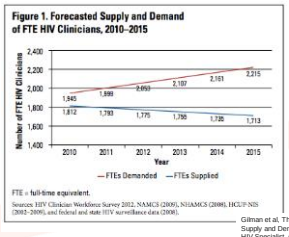
What about providers?

Physician Shortage

- "US Healthcare system is in a period of marked uncertainty."
- >1/3 of all physicians will be >65 in the next 10 years
- Shortage between 40,800 and 104,900 physicians by 2030
- Caps placed 20 years ago on federal Medicare funding for residency training makes it difficult to expand GME.
- Congress needs to raise the caps to train more physicians.

Kirsch et al, JAMA May 2017

Bottom line….



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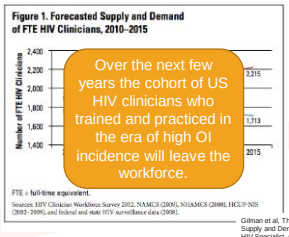


Over the next few years the cohort of US HIV clinicians who trained and practiced in the era of high OI incidence will leave the workforce.

Gilman et al, The Clinician HIV Workforce in the United States, Supply and Demand Projections from 2010-2015. HIV Specialist, Aug 2016. www.aahivm.org

OIs in 2018

- Jesse, a thirty-six-year-old male, arrives at the clinic as a new patient. He has never been in care before.
  - **HPI**: Has had increasing fatigue, weight loss, chills, some night sweats, some headache when he climbs stairs. He has a chronic cough that he has had "for years". No blurred vision, no GI symptoms, does admit to missing some appointments.
  - **SH**: Grew up in New York, MSM, sexual debut at age 14. First tested positive in June 2018. Thinks he had a negative test a few years ago. Now lives in Memphis, unemployed. He occasionally drinks whiskey (6 shots a week), daily marijuana and occasionally injects opioids that he buys on the street. Last injected about 6 weeks ago.

Jesse

- **PE**: T99.2, RR 14. BP 112/74 WT 142 LB BMI 20.6 Pulse O2 93%; thin alert, slightly slow response time, lungs are clear. Abnormal findings include 1/3 short term recall, absent achilles reflexes, increased patellar reflexes. Fine motor and gait are impaired. Skin is dry and some scaling along scalp line. Fundoscopic exam is limited but wnl.
- **Labs**:
  - H/H 12.4/35%; WBC 2.3, Creatinine .67, Electrolytes wnl. LFTs with very minimally elevated AST and ALT.
  - HIV-1 RNA 643,221 copies/ml, CD4 cell count 86/4%. Trep Ab and T-spot negative. Toxoplasma, HBV, and HAV serologies show past infections, HCV Ab negative. HIV 1 genotype shows wild type virus.

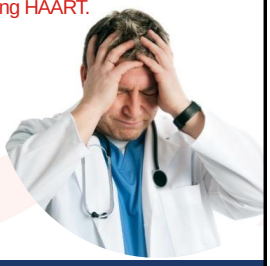
ARS Question 1: What is your next step?

1. Start patient on a coformulation of three antiretrovirals, PCP prophylaxis and follow up closely.
2. Obtain a more detailed HPI and ROS and then decide next steps.
3. Obtain CXR and if no acute disease, start HAART and prophylaxis.
4. Have the patient meet with the pharmacy team to discuss treatment goals, adherence and possible barriers to care and then arrange quick follow up with provider to start HAART.
5. Initiate a fairly extensive work up to diagnose any active OIs.

ARS Question 2: Your supervising attending rolls his eyes and glares at you when you suggest starting HAART.

He thinks you should work up possible OIs before starting HAART.

What next steps would you take before starting HAART?



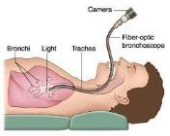
ARS Question 2: What next steps would you take before starting HAART?

- 1) Induce sputum for PCP, get OI tests (Cryptococcal Ag, Histo Ag. AFB, CMV PCR).
- 2) Obtain pulse O2 sat% on exertion, if abnormal then consider PCP, do 1) as well.
- 3) Get a room air ABG if possible, if not consider high resolution CT scan of chest and if abnormal consider PCP. Do 1) as well.
- 4) Get a better sexual history and then do 1), add treatment of STIs as needed.

- A panel of tests are ordered to evaluate for an active OI;
  - Serum Cryptococcal Ag, Urine Histoplasma AG, Toxoplasma serology, T-Spot, Blood culture for AFB, plasma CMV PCR and a CXR which is read as no acute changes.
- A room air ABG is obtained which shows a pO2 of 67mm and a large A-a gradient.

ARS Question 3: What is the next step?

1. Treat for PJP with high dose TMP-SMX;
2. Treat for PJP with high dose TMP-SMX and prednisone
3. Arrange further testing to diagnose cause of pneumonitis.
4. Await other OI related test results to come back before deciding on next course.



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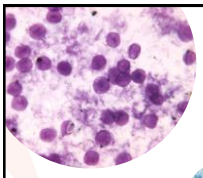

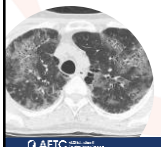

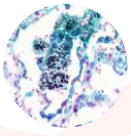

Patient is admitted and undergoes bronchoscopy with BAL.

GMS stain is positive for pneumocystis.

PJP

Organism: P. jiroveci; ubiquitous, 2/3 children seropositive by age 4;

Transmission: probable airborne, reactivation>new acquisition;

Incidence: 70-80% of AIDS pts. prior to prophylaxis, now most common new ADE or in untreated patients.

Prognosis: lethal if untreated; advanced HIV and severe PCP carry 20-40% mortality.

Risk factors: CD4<200 cells/mm^3 (90%), CD4 <14%, thrush, wasting, recurrent pneumonia, elevated HIV-1 RNA

PJP

- Clinical presentation depends on duration of illness, concurrent morbidities and patient's activity level.
- Early disease: fever, dry cough, some dyspnea on exertion, normal CXR and pO2; O2 % sat is not ideal marker; *(RA ABG is critical!)*
- Moderate to severe disease: fever, non-productive cough, progressive dyspnea, chest discomfort, headache; associated advanced HIV disease symptoms;
- Pneumothorax in a patient at risk should be considered PCP until proven otherwise.
- Imaging: early disease may have normal CXR; "classic" findings are butterfly-interstitial pattern, all radiologic patterns have been reported. High resolution CT can help determine appropriate course.
- Newer diagnostic options like PCR for PJP and serum 1,3B-D-glucan assay do add much to the work up and **treating presumptive PJP is rarely appropriate.**

AETC Southeast

PJP

- Clinical presentation depends on duration of illness, concurrent morbidities and patient's activity level.
- Early diseas… …ormal CXR and pO2; O2 % sat is …
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- Newer diagnostic options like PCR for PJP and serum 1,3B-D-glucan assay do add much to the work up and **treating presumptive PJP is rarely appropriate.**

You must prove to yourself that the febrile patient with AIDS on no medications does not have PCP.

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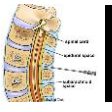
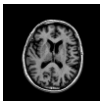
ARS Question 4: Your attending calls you on your day off and asks if you noticed that the patient's serum Cryptococcal Ag is positive and his CMV PCR is 1,234 copies/ml.





Your next step is:

1. Arrange lumbar puncture and follow up results;
2. Obtain imaging of brain and if OK, do 1.
3. Arrange emergent ophthalmology evaluation and arrange 2. as well.
4. await completion of treatment of PJP before considering initiation of treatment for cryptococcus or CMV.

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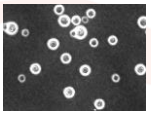
ARS Question 4: Your next step is:

1. Arrange lumbar puncture and follow up results;
2. Obtain imaging of brain and if OK, do 1.
3. Arrange emergent ophthalmology evaluation and arrange 2. as well.
4. await completion of treatment of PJP before considering initiation of treatment for cryptococcus or CMV.

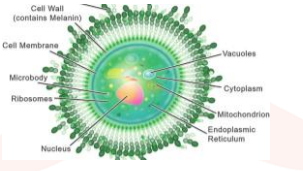
Cryptococcal disease

- Patient has a non-contrasted CT scan of the head which only shows some cerebral atrophy.
- LP yields: OP of 24 cm, 4 WBCs, Glucose is normal and protein is slightly elevated. Indian ink and cryptococcal Ag are positive.
- He is admitted for induction therapy for cryptococcal meningitis.



Cryptococcal Meningitis

- C. neoformans is an encapsulated yeast, inhaled into the small airways where it usually causes sub-clinical disease; dissemination to the CNS is not related to pulmonary response.
- C. neoformans produces no toxins and evokes little inflammatory response. The main virulence factor is the capsule.



Cryptococcal Meningitis

- Clinical manifestations:
  - headache (70-90%), fever (60-80%), malaise (76%), stiff neck (20-30%), photophobia (6-18%), seizures (5-10%) nausea. *(true meningismus is rare)*
- Average duration of symptoms is 30 days.
- Predictors of poor outcomes are altered mental status, increased opening pressure, WBC<20 cells/mm^3.
- Diagnosis made by CSF examination with india ink (74-88%), Crypto Ag serum/CSF (99%), CSF culture.
- Level of Crypto Ag is not indicative of severity of disease nor a marker of response to therapy. Serum Crypto Ag can rule out clinical disease in HIV positive but not negative patients.

Jesse

- Jesse is started on induction therapy with liposomal amphotericin therapy in addition to oral flucytosine. Repeat LP reveals a normal OP and similar indices. He does well and is discharged home on oral fluconazole.
- Two days prior discharge he is started on HAART.
- Ten days after discharge he presents to his clinic follow up appointment, feeling better, minimal headache, increased appetite, gaining weight.
- Ten days later he calls the service complaining of increased headache, feeling poorly.

Jesse

ARS Question 5: Appropriate next step would be:

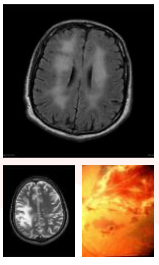
1. Repeat serum cryptococcal antigen, CMP, CD4 count,
2. Add corticosteroid therapy to treat presumptive IRIS,
3. Bring patient in for imaging of his brain, repeat LP and follow up;
4. Continue to monitor closely in clinic.

Cryptococcal disease and HAART

- Initiation of HAART in a patient with active cryptococcal disease can cause immune reconstitution inflammatory syndrome in up to 30% of patients.
- Recommendations are to delay from 2-10 weeks prior to initiating HAART.
- Signs of IRIS should be monitored and evaluated immediately.

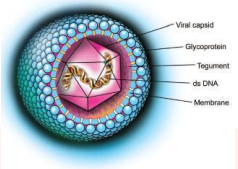
CMV

- Jesse is evaluated by the ophthalmologist and no signs of CMV retinitis are seen.
- A contrasted MRI of the brain shows some mild white matter disease.



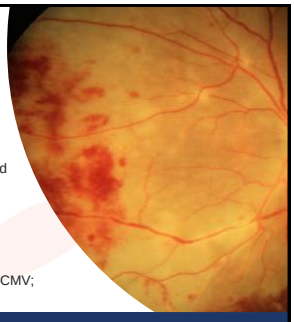
CMV Disease

- Disseminated viral infection which causes disease in advanced (CD4 <50 cells/mm^3) AIDS.
- CMV seropositivity highest in MSM and IVDU;
- Usually reactivation disease;
- Several reports of IRIS related disease;
- Clinical manifestations are related to end-organ damage:
  - Retinitis (30% of AIDS patients)
  - Colitis (5-10% of AIDS patients)
  - Esophagitis (<10% of AIDS patients)
  - Neurologic disease (<5% of AIDS patients)



HCMV Human Cytomegalovirus

CMV Retinitis



- Most common presentation of CMV infection;
- >60% with unilateral disease; will progress to second eye if untreated;
- Symptoms include floaters, scotomata, field cuts, decreased acuity;
- Progresses rapidly, in "stops and starts", can be sight threatening in 24 hours;
- Painless, rarely associated with new systemic symptoms;
- Several reports of IRIS and IRU related to CMV;

CMV Disease

Diagnosis:

- Retinal disease: recognition of classic findings in at-risk patient, serology not useful; viremia negative in 30% of patients.
- GI disease: biopsy with histology demonstrating intranuclear inclusion bodies with inflammatory reaction at edge of ulcer;
- Culture results are not adequate to demonstrate active disease;
- Neurologic disease may depend on CSF findings or brain biopsy.

ARS Question 6: Given that Jesse has detectable CMV viremia:

Would you;

1. Start CMV treatment with oral medication along with HAART after treatment of his cryptococcal disease;
2. Start CMV treatment and delay starting HAART another two weeks;
3. Start HAART once cryptococcal treatment has been delayed appropriately.

ARS Question 6: Given that Jesse has detectable CMV viremia:

Would you;

1. Start CMV treatment with oral medication along with HAART ccal disease;
2. Start CM g HAART another two wee
3. Start HAART once cryptococcal treatment has been delayed appropriately.

Not all opportunistic infections have to be treated but they should be monitored once HAART has been initiated.

Malcolm

- 61-year-old male with longstanding HIV infection, intermittent treatment due to competing issues of poverty, IDU and schizo-affective disorder is admitted through the ED with severe malaise, hypotension, fever, diarrhea, pancytopenia.
- PE reveals cachectic male, somewhat obtunded, significant periorbital swelling with discoloration left upper eyelid. He has 2+ left lower extremity edema, scattered crackles on lung exam.
- CT of the chest and abdomen shows diffuse adenopathy in axillary, perihilar and inguinal distribution. Scattered nodular infiltrates in both lung fields with effusion in left base.

Malcolm

- Labs reveal:
  - Hgb/Hct 8.1/23; WBC 1.1, Plt 64,000
  - Creatinine 2.0, LFTs mildly elevated
  - CRP 34, LA 1.0
  - CMV PCR 640 copies/ml; EBV PCR 2320 copies/ml, HHV 6 undetectable, HHV8 2320 copies/ml;
  - UA shows TNTC WBC, bacteria; urine and blood cultures pending.
  - Serum cryptococcal antigen is positive, titer pending.
- Patient is transferred to the MICU, intubated and fluid support, broad spectrum antimicrobials are initiated.

Malcolm

ARS Question 7: Which pathogen could be the cause of Malcom's entire clinical presentation?

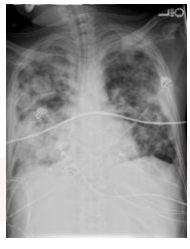
1. Cryptococcus neoformans
2. E. coli
3. HHV8
4. CMV
5. EBV
6. HHV6

One new (old) pathogen

- Human Herpesvirus-8
  - Etiologically associated with all forms of Kaposi sarcoma (KS)
    - Still the most common cancer PLWHA in the U.S.
  - Also associated with:
    - Primary Effusion Lymphoma (PEL)
    - Multicentric Castleman's Disease (MCD)
    - KSHV inflammatory cytokine syndrome (KICS)
  - KS is still the most common clinical manifestation of HHV-8 infection.
    - PEL, MCD and KICS are much less common and are seen usually in the setting of extreme immune suppression.
  - The risk of developing KS is inversely proportional to the CD4 cell count but recent reports suggest an increase in immune competent patients.
  - Tissue diagnosis is still critical, peripheral blood HHV-8 PCR is not helpful.

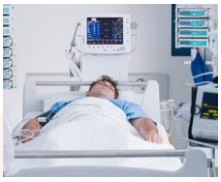
Carlos

- 38 year old Guatemalan HIV + male admitted for fever, chills, weight loss, abdominal pain, pancytopenia with splenomegaly.
- He reports increasing fatigue and progressive dyspnea.
- CD4 count is 32 cells/mm^3; HIV 1 RNA is 680,343 copies/ml.
- Imaging is consistent with multifocal pneumonia.
- He is admitted to the ICU.



Carlos

- Patient initially requires volume support and pressors.
- ID, pulmonology, hematology and general surgery are consulted.
- Imaging also reveals massive splenomegaly with prominent mass effect on adjacent organs.
- Differential includes: infectious (AFB, fungal, EBV, malaria), lymphoma, myeloproliferative disorders, and rheumatologic disease.
- He is treated with broad spectrum antibiotics, antivirals and IV IgG is also started.
- Work up including BM biopsy, cultures, HHV 8 are negative.
- Hematologic work up reveals elevated ferritin, IL2R and other findings consistent with HLH; massive splenomegaly thought to be related to underlying lymphoma.
- Plan is to start HLH protocol, splenic embolization before diagnostic/therapeutic splenectomy.

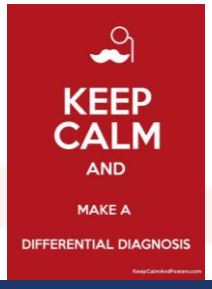


Carlos

- Patient is readmitted emergently to the ICU from a hematology clinic visit for sepsis, pneumonia.
- Comprehensive infectious work up is again negative.
- Patient responds to antibiotics, fluids, and is discharged home for elective splenectomy when appropriate.
- Working diagnoses are AIDS, HLH, splenomegaly secondary to underlying malignancy and resolving HCAP.

Carlos

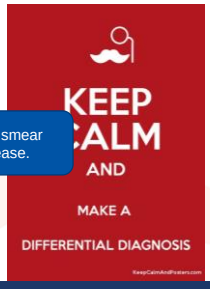
- During his work up the following diagnoses were considered:
  - Bacterial sepsis, PCP, disseminated AFB (MTB, MAC) , fungal (Cryptococcosis, Histoplasmosis, Coccidiomycosis, Aspergillosis), and viral infections (EBV, CMV, HHV 8) strongyloidiasis, malaria.
- He received PCP prophylaxis, empiric therapy directed at fungal and bacterial pathogens.
- A diagnosis was made of HLH based on lab (ferritin, cytopenia) and clinical picture.
- He received IVIgG for his splenomegaly.



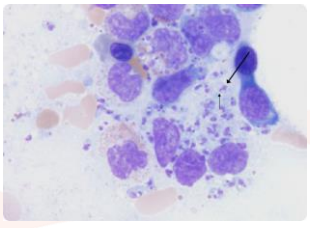
Carlos

- During his work up the following diagnoses were considered:
  - Bacterial sepsis, PCP, disseminated AFB (MTB, MAC) , fungal (Cryptococcosis, Histoplasmosis, Aspergillosis), HHV 8) strong
- He received PC therapy directed at fungal and bacterial pathogens.
- A diagnosis was made of HLH based on lab (ferritin, cytopenia) and clinical picture.
- He received IVIgG for his splenomegaly.

A routine peripheral blood smear revealed underlying disease.



Leishmania on Peripheral Blood Smear



Geographic OIs

Guidelines

- Malaria
  - Sub-Saharan Africa, SE Asia
- Penicilliosis marneffei
  - SE Asia, South China
- Leishmaniasis
  - Tropics, sub-tropics and Southern Europe
- Chagas Disease
  - Latin America
- Isosporiasis (Cystoisporiasis)
  - Tropical and Sub-tropical

Additional

- MTB
  - Everywhere
- Histoplasmosis
  - Ohio and Mississippi River Valleys, Central and South America
- Coccidiomycosis
  - Southwestern US, Mexico and South America

So what is new?

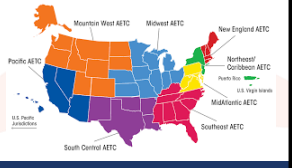
- There are less patients presenting with OIs but about 20% of newly diagnosed are at risk for developing an OI.
- Fewer practicing clinicians have extensive experience diagnosing and treating OIs.
- There have been few new technologies that change evaluation of OIs significantly.
- Initiation of HAART in the setting of an active OI must be timed appropriately.
- IRIS must be anticipated and evaluated when appropriate.
- Primary and secondary prophylaxis guidelines are updated, as well as when to discontinue prophylaxis.

So what is old?

- The main pathogens: PJP, MAC, Cryptococcus, MCV, Toxoplasma and bacterial pneumonias still account for most of the serious OIs.
- More harm will likely be done by missing common OIs rather than the rare exotic:
  - PJP: think of it, check oxygenation, don't treat empirically.
  - Cryptococcal disease: no meningismus, no inflammatory component in the CSF;
- Prioritize the work up in a immune suppressed patient with multiple complaints and abnormal lab results.

Resources

- Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents https://aidsinfo.nih.gov/guidelines
- Regional AETCs: SEAETC.com
- HIV Essentials Paul Sax (2017)



Question-and-Answer